Lederle

QB

AN ADVANCE IN PARENTERAL

Liver Therapy

A REFINED AND MORE CONCENTRATED
SOLUTION OF LIVER EXTRACT FOR

Intramuscular Injection

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DURING the past five years many cases of pernicious anemia have been successfully treated by the oral administration of liver and liver extract.

Not infrequently, pernicious anemia patients come into hospitals critically ill and it has been necessary to resort to administration by stomach tube of either liver or liver extract. Occasionally, it has been necessary to give supportive transfusions to maintain such patients until the effects of liver or liver extract were manifested.

LIVER FRACTIONS FOR INTRAMUSCULAR INJECTION

Collaborating with Dr. W. P. Murphy of the Peter Bent Brigham Hospital, Boston, Massachusetts, the Lederle Laboratories have developed and are prepared to supply a refined and concentrated solution of liver extract, containing the fraction G of Cohn[1] suitable for intramuscular injection in the treatment of pernicious anemia.

Solution Liver Extract (*Lederle*) for intramuscular administration may be employed to advantage in the treatment of all cases of pernicious anemia. It is especially indicated in the treatment of the critically ill patient and because of the rapid response and ease of administration, Murphy[2] suggests that the intramuscular injection of Solution Liver Extract will replace the use of either transfusion or stomach tube in such cases. The intramuscular injection of Solution Liver Extract (*Lederle*) is also of great value in the treatment of pernicious anemia patients who find it difficult to regularly ingest or retain adequate amounts of liver or liver substitutes. Intramuscular injection of Solution Liver Extract is likewise indispensable in the treatment of those cases which have not favorably responded to intensive oral administration of liver, liver extract, or substitutes. In this resistant class, there are many patients in whom the red blood cell count remains in the neighborhood of 3.5 million even with daily oral doses of liver extract derived from 1000 grams of liver.

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[1] Cohn, E. K., Minot, G. R., Fulton, J. R., Ulrichs, H. F., Sargent, F. C., Weare, J. H. and Murphy, W. P.: The Nature of the Material in Liver Effective in Pernicious Anemia. I., *Journal of Biological Chemistry,* July, 1927, Vol. 74, lxix.

[2] Murphy, W. P.: The Parenteral Use of Liver Extract in Pernicious Anemia, *Jour. A. M. A.,* 1932, Vol. 98, p. 1051.

MURPHY[2] reports the satisfactory treatment of six patients of this resistant type by the intramuscular injection of the material obtained from 100 grams of liver at intervals of 3 to 7 days.

The use of SOLUTION LIVER EXTRACT (*Lederle*) is also suggested for the treatment of sprue. The anemias of sprue respond to liver therapy in about the same manner as pernicious anemia. It is possible that in the large field of secondary anemias there may be some groups which will be benefited by the injection of Solution Liver Extract.

MURPHY[2] and CONNERY and GOLDWATER[3] noted pronounced increases in white blood cells and platelets following the intramuscular injection of Solution Liver Extract which suggests the use of the parenteral extract in diseases in which either of these blood elements are below normal levels.

INITIAL TREATMENT

Although some cases of pernicious anemia in relapse have responded to intramuscular injections of Solution

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[3] CONNERY, J E. and GOLDWATER, L. J.: Parenteral Use of Liver Extract in Pernicious Anemia, *Jour. A. M. A.*, 1932, Vol. 98, p. 1060.

Liver Extract obtained from 100 to 200 grams or less, these amounts may not, in all cases, represent optimum dosage. In this connection, MURPHY[2] states that in the experience gained from the treatment of 30 patients reported in his paper the most satisfactory use of the parenteral treatment is the intramuscular injection of large or optimum amounts of liver extract representing the material obtained from 300 to 400 grams of liver during the initial treatment of a patient in relapse. CONNERY and GOLDWATER[3] likewise recommend a series of 3 or 4 successive daily injections, each containing the material obtained from 100 grams of liver.

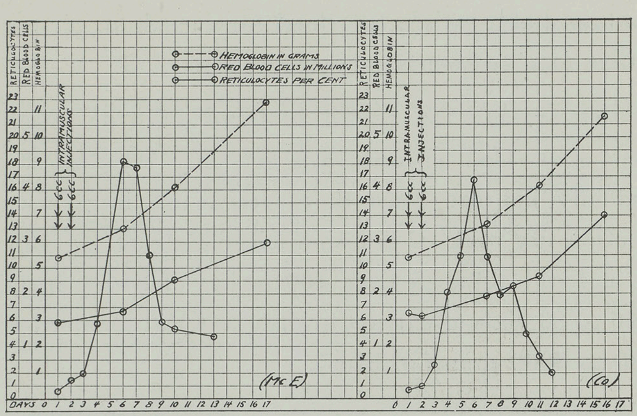
SUBSEQUENT TREATMENT AND MAINTENANCE

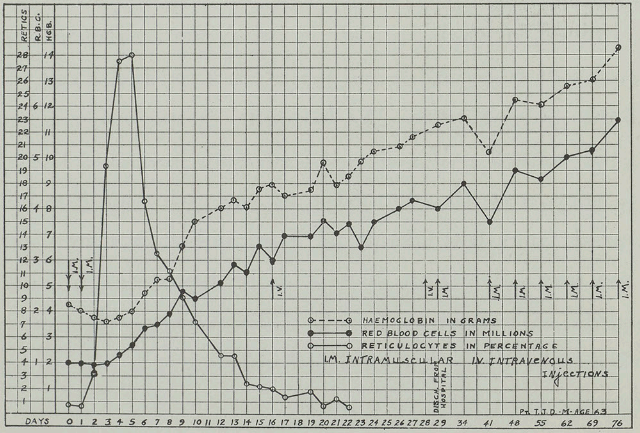
After a patient has received the initial series of injections and the red blood cells have subsequently reached their maximum from this dosage, treatment should be resumed. In non-hospitalized cases, CONNERY and GOLDWATER[3] recommend that treatment be resumed one week after the initial series instead of waiting for the maximum red cell increase. In the series of cases reported by MURPHY and by CONNERY and GOLDWATER in which remissions have been initiated by the use of SOLUTION LIVER EXTRACT (Lederle), there is evidence that the weekly injection of the contents of one vial containing material obtained from 100 grams of liver is adequate to complete and maintain a satisfactory state of remission in the average case. There are undoubtedly cases which will be maintained at a satisfactory level for a much longer period of time (ten to twenty or more days).

Cases are now on record in three different hospitals which show that patients are not only maintained but gradually improve when they receive one intramuscular injection per week of Solution Liver Extract (representing material obtained from 100 grams of liver), in place of 20 to 60 vials of extract orally (material obtained from 2000 to 6000 grams of liver).

In complicated cases and those with extensive neurological involvement, dosage may be larger and must be determined for each patient. In brief, the treatment should be sufficient to establish and maintain a red blood cell count of 5,000,000 or more. As MURPHY points out in discussing the refined and concentrated Solution Liver Extract it is very easy to administer at one injection the active material from 100 grams of liver and it is very difficult to see any advantage in the daily injections of smaller amounts of potent material. The weekly injection also obviates the daily use of the hypodermic needle which is generally distasteful to patients.

The following charts from the service of Dr. Murphy illustrate the nature of the reticulocyte, red blood cell and hemoglobin response obtained by the use of SOLUTION LIVER EXTRACT, Refined and Concentrated.





REACTIONS

The undesirability of intravenous therapy has been pointed out by a recent editorial in the *Journal of the American Medical Association*[4] and subsequently in a report of the Council on Pharmacy and Chemistry.[5] The intravenous administration of Solution Liver Extract and similar products has at times produced reactions, which, although not serious in nature have been disturbing to both the patient and the physician. MURPHY treated some of his cases by intravenous administration of Solution Liver Extract. He found no advantage in this form of administration and makes the following statement:

> " . . . the risk entailed in the intravenous as opposed to intramuscular injection must be borne in mind, and as the results obtained in the cases reported show no advantage in the intravenous injections, it would seem advisable to use the intramuscular route of injection generally."

We, therefore, recommend only the intramuscular administration of SOLUTION LIVER EXTRACT (*Lederle*) Refined and Concentrated.

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[4] Safe Products for Parenteral Administration, Editorial, *Jour. A. M. A.,* 1931, Vol. 97, p. 1230.

[5] Intravenous Therapy, Report of Council on Pharmacy and Chemistry, *Jour. A. M. A.,* 1932, Vol. 98, p. 1165.

With the early preparation of Solution Liver Extract, patients frequently complained of pain following the injection. However, with the refined and concentrated product, injections are made without any appreciable discomfort to the patient. In this connection, Connery and Goldwater state:

> "As far as can be determined, it would seem that the pain occasioned by Solution Liver Extract differs in no respect from that which occurs in other intramuscular injections"

and

> "in our series of cases no patient has expressed a desire to forego this treatment because of the pain."

Murphy likewise states:

> "The extract has been administered to this series of patients without a reaction of importance."

SENSITIZATION OF PATIENTS TO LIVER

There have been a few reports of allergic conditions following the oral ingestion of liver and liver extracts. During the time in which Solution Liver Extract (*Lederle*) has been used clinically, we have been frequently asked concerning the possibility of sensitizing patients to this preparation. While Solution Liver Extract (*Lederle*) Refined and Concentrated is practically protein-free and it was felt impossible to cause any characteristic allergic reaction, the Laboratory carried on extensive experiments with guinea pigs, the results of which demonstrated that it would be practically impossible to produce any degree of sensitiveness on the part of the patient to SOLUTION LIVER EXTRACT (*Lederle*). CONNERY and GOLDWATER state that:

> "In a series of more than 500 intramuscular injections no disturbances were noted which were in any way suggestive of allergic reaction."

MURPHY, however, believes it desirable in the case of patients with marked allergic history that a very small injection be made to test the patient and thus entirely to avoid any possibility of an allergic reaction.

EFFECTS PRODUCED BY INTRAMUSCULAR ADMINISTRATION

During the five years of liver therapy, it has become generally recognized that an increase of the reticulocytes in the peripheral circulation is the earliest evidence of a favorable response to the feeding of liver or potent liver fractions. This stimulation of the bone marrow by material absorbed from liver and liver extract with its resulting increase in reticulocytes constitutes the most rapid means of estimating the potency of liver fractions and evaluating them in terms of whole liver.

The reticulocyte response may be influenced by several factors:

1. Severity of the anemia.
2. Amount of liver or liver extract administered.
3. Potency of the preparation.
4. Method of administration.
5. Complicating factors.

The administration of liver extract by intramuscular injection causes a more prompt increase of reticulocytes than has hitherto been obtained by other forms of liver therapy.

Failure to obtain the maximum reticulocyte response may be due either to inadequate amounts of potent material or to material of questionable potency. Complicating factors, such as infection, old age, disease, etc., also tend to depress the reticulocyte response.

RED CELLS AND HEMOGLOBIN

A survey of a series of cases treated with Solution Liver Extract shows that there is usually a more rapid increase in the number of red blood cells and in the hemoglobin content than has heretofore been obtained by other methods of liver therapy. Following the initial series of injections, it has even been observed that in a period of two weeks the red blood cells have increased to three times the number present at the time of instituting liver therapy. Likewise, hemoglobin values have more than doubled in this short interval.

In patients treated with intramuscular injections of Solution Liver Extract the general clinical improvement is comparable to the more rapid increase in the number of red blood cells and in the hemoglobin content.

ADVANTAGES

The treatment of patients with pernicious anemia by the intramuscular injection of SOLUTION LIVER EXTRACT (*Lederle*) has several advantages over the earlier form of treatment with liver or various substitutes administered orally.

1. Ease of administration to critically ill patients.
2. Certain dosage.
3. Rapid response.
4. Successful treatment of cases refractory to substances administered orally.

5. Possible beneficial results in nervous involvement.
6. Economy.
7. Relief of patients from necessity of continued oral administration.

PACKAGES

Lederle SOLUTION LIVER EXTRACT, Refined and Concentrated, for Intramuscular Use, is supplied in boxes of three vials, each vial containing in a volume of 3 c.c. the active material obtained from 100 grams of liver. This preparation contains 0.5 per cent phenol as a preservative.

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